and alterations have been made in the specification. The claims have been amended by amending claims 1-10. The applicants hereby request re-examination and reconsideration of the application in view of the foregoing amendments.

In accordance with the United States Patent and Trademark Office Rule 1.99, it is hereby requested that the following additional reference be made of record in the Patent and Trademark Office file relating to the application identified above.

German Offenlegungsschrift 2 218 644

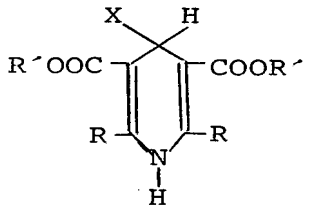
A copy of this reference is enclosed.

This reference does not disclose the particular 1,4-dihydropyridines which are claimed in the instant application. It is respectfully submitted that the present invention is not disclosed by this reference and is not obvious in view of it.

Claims 1-11 stand rejected under 35 U.S.C. §103 as unpatentable over the Bossert et al. patent. The Examiner has stated in the Official Action that the Bossert et al. patent discloses compounds which generically include the claimed compounds, and that it specifically discloses analogues of 1,4-dihydropyridine-3,5-dicarboxylates. The Examiner also stated that the reference disclosed the same utility and pharmaceutical preparations and that this raised the presumption of obviousness. However, the claims are believed to be allowable because it is submitted that the reference would not render the claimed invention obvious to a person of ordinary skill in the art.

107

The Bossert et al. patent relates to symmetrical di(carboxylic acid-esters) of 1,4-dihydropyridines of the formula



wherein R is hydrogen or alkyl of 1 to 3 carbon atoms, R´ is alkyl or alkylene of 1 to 6 carbon atoms interrupted by one or more oxygen atoms or substituted hydroxyl, and X is pyridyl, phenyl, pridyl substituted by halogen, 1 or 2 lower alkyl, lower alkoxy, nitro, amino, acylamino or alkylamino or phenyl substituted by halogen, 1 or 2 lower alkyl, lower alkoxy, nitro, amino, acylamino or alkylamino and pharmaceutically acceptable non-toxic salts thereof.

The applicants submit that the instantly claimed invention is neither recited in nor suggested by the Bossert et al. patent. There is not a single instance therein where the presently claimed compounds are mentioned. Columns 2, 4, 5, and 6 in the reference offer specific examples of the 1,4-dihydropyridine derivatives which are claimed in the Bossert et al. patent. All are plainly compounds in which R´ is an alkoxyalkyl, and are, for that reason, not suggestive of anything claimed in this case.

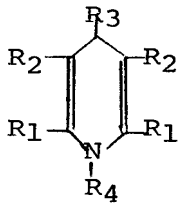
The only reference in the Bossert et al. patent to any other type of compound appears in claim 1 of the Bossert et al. patent which mentions compounds in which R´ is lower alkyl. Nifedipin, referred to in Table 2 of this application is such a compound. Nifedipin differs from the claimed com-

108

pounds in the substitution on the benzene ring. Nifedipin is a 2-nitro compound, while the claimed compounds are 2,3-substituted, and do not involve nitro substitution. As can be seen from Table 2, Nifedipin is substantially less selective than the compounds which are claimed.*

Claims 1-11, stand rejected under 35 U.S.C. §103 as unpatentable over the Loev et al. patent. The Examiner has stated in the Official Action that the Loev et al. patent discloses closely related 1,4-dihydro-2,6-dimethyl-4´ substituted aryl-3,5-pyridinedicarboxylates. The Examiner also stated that the reference demonstrates the same utility and pharmaceutical preparations and that this gave rise to a presumption of obviousness. However, the claims are believed to be allowable because it is submitted that the reference would not render the claimed invention obvious to a person of ordinary skill in the art.

The Loev et al. patent relates to symmetrical substituted 1,4-dihydropyridines-3,5-di(carboxylic acid-esters) of the formula



in which R_1 is lower alkyl having 1-6 carbon atoms; R_2 is COOR´ or COR"; R_3 is phenyl, halophenyl, dihalophenyl, lower alkylphenyl, di-lower alkyphenyl, tri-lower alkylphenyl, lower alkoxyphenyl, di-lower alkoxyphenly, tri-lower alkoxyphenyl, trifluoromethylphenyl, benzyl, styryl, furyl, thienyl, pyridyl, or pyrrolyl, said lower alkyl and lower alkoxy

*We point out that by reason of the amendments which are made herein, the compounds of examples 4, 10 and 19 are not within the scope of the claims.

109

groups having 1-4 carbon atoms; R_4 is hydrogen or lower alkyl having 1-6 carbon atoms and R' and R" are lower alkyl having 1-6 carbon atoms.

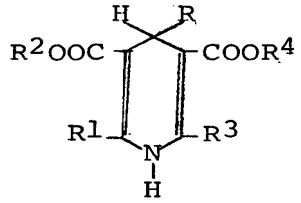
The applicants submit that the instantly claimed invention is neither recited in nor suggested by the Loev et al. patent. There is not a single instance where the presently claimed compounds are mentioned therein. Columns 5, 6, 7, and 8 in the Loev et al. patent demonstrate specific examples of the 1,4-dihydropyridines-3,5-di(carboxylic acid-esters) which are claimed in the Loev et al. patent. The Examiner's attention is directed to the fact that the 1,4-dihydropyridines-3,5-di(carboxylic acid-esters) which are exhibited in those exapmles are not the same as those new compounds which are claimed in the instant application. All of the compounds of the examples are substituted at the 2,6-positions of the pyridine rings - where the claimed compounds are unsubstituted; none of the compounds disclosed in Loev et al. show 2,3 substitution in the benzene ring. The Examiner points to nothing which suggests a modification of the Loev et al. compounds which bears on what the applicants have discovered. Moreover the Loev et al. compounds are significantly less selective that those which are claimed.

Claims 1-11 stand rejected under 35 U.S.C. §§102 and 103 as unpatentable over the Meyer et al patent. The Examiner has stated in the Official Action that the reference discloses a limited number of 1,4-dihydropyridines which clearly read on the instant claims. The Examiner also stated that the reference demonstrated the same utility and pharmaceutical preparations and that closely related analogues raised the presumption of obviousness. However, the claims are believed to be allowable because it is submitted that the

110

reference would not render the claimed invention old or obvious to a person of ordinary skill in the art.

The Meyer et al. patent relates to asymmetric esters of substituted phenyl-1,4-dihydropyridines of the formula



wherein R is phenyl, unsubstituted or substituted by up to three substituents selected from the group consisting of lower alkyl, lower alkoxy, halogeno, trifluoromethyl or carbo-(lower alkoxy); R^1 and R^3, independent of the other, is hydrogen or lower alkyl; R^2 is a member selected from the group consisting of lower alkyl, lower alkenyl, lower alkynl, or lower alkoxy (lower alkyl); R^4 is a member different from R^2 selected from the group consisting of lower alkenyl, lower alkynyl or lower alkoxy (lower alkyl), or a pharmaceutically acceptable acid addition salt thereof.

The applicants submit that the instantly claimed invention is neither recited in nor suggested by the Meyer et al. patent. The Examiner's assertion of anticipation under 35 U.S.C. §102 is noted; however we have been unable to find any basis for it. Columns 4, 7, 8, and 9 in the reference demonstrate a number of specific examples of the asymmetric esters of the substituted phenyl-1,4-dihydropyridines which are claimed in the Meyer et al. patent. None of the compounds disclosed are within the scope of the claims in the instant application.

Viewed from the standpoint of 35 U.S.C. §103, it is clear that the Meyer et al. compounds, like those of Loev et al.

111

are substituted at the 2,6 position of the pyridine ring and lack the 2,3 substitution on the phenyl ring which characterizes the claimed compounds. Again the Examiner points to no facts suggesting any modification of what the references disclose, and the claimed compounds are significantly more selective.

Claims 5-7 stand rejected under 35 U.S.C. §112, second paragraph. The Examiner has stated in the Official Action that the method claims should recite a mode of administration and the effective amount of the active compounds. In light of this rejection, claim 5 has been rewritten.

Claims 8-11 stand rejected under 35 U.S.C. §112, second paragraph. The Examiner has stated in the Official Action that pharmaceutical composition claims lack propriety when a composition alludes to one or more active compounds of a Markush group when support in the specification is only provided for one. In light of this rejection, claim 8 has been amended.

Based on the foregoing amendments and the distinctions set forth, it is submitted that the claims are in condition for allowance. Reconsideration of the rejections and objections is requested. Allowance of the claims at an early date is solicited.

Respectfully submitted,

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112